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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/734,628	CHINNAIYAN ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76,80,82-84,87,91 and 96-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76, 80, 82-84, 87, 91, 96-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 4/1/04, is acknowledged.

2. Claims 76, 80, 82-84, 87, 91-92 and 96-98 are pending and under examination.

3. In view of the amendment filed on 4/1/04, only the following rejections are remained.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 76, 80, 82-84, 87, 91-92 and 96-98 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 9/24/03. This is a New Matter rejection.

The phrases "imaging agent" claimed in claims 76, 80, 87and 92, lines 1-3 represents a departure from the specification and the claims as originally filed.

Applicant's arguments, filed 4/01/04, have been fully considered, but have not been found convincing.

Applicant is broadening the "bioluminescence imaging" agents disclosed on page 8, lines 11-22, page 14, lines 10-15, page 18 and page 19 by reciting "imaging agent" in the claims violating the written description requirement. Applicant is creating a generic imaging agents. In re Wilder, 736 F.2d 1516, 222 USPQ 369 (Fed. Cir. 1984), the court held that the generic invention was not supported by the original patent's disclosure in such a way as to indicate possession, as of the original filing date, of that generic invention.

6. Claims 87, 92, 96 and 97 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for *in situ* or *in vivo* imaging of a tumor neovasculature in an individual comprising administration a chimeric polypeptide wherein the chimeric molecule comprises bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO:1 does not reasonably provide enablement for a method of *in situ* or *in vivo* imaging, comprising providing cells, any chimeric polypeptide and an imaging agent wherein said chimeric polypeptide comprises an illumination domain, and any target recognition

domain, wherein said illumination domain comprises a luciferase, wherein said target recognition domain "comprises" any "**RGD sequence**", wherein said imaging agent is luciferin in claim 87; a method of imaging comprising providing cells, a chimeric polypeptide, an imaging agent, wherein said chimeric polypeptide comprises an illumination domain, and a target recognition domain, wherein said illumination domain comprises a bioluminescent polypeptide, wherein target recognition domain "comprises" any "**RGD sequence**" in claim 92. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action mailed 9/24/03.

Applicant's arguments, filed 4/01/04, have been fully considered, but have not been found persuasive.

Applicant submits that the specification supports enablement of various RGD sequence motifs. Applicant further argues that the specification supports the use of RGD sequences beyond SEQ ID NO: 1. For example, the Specification, at page 15, lines 20-25, incorporate references pertaining to the application of various RGD sequences within empirical settings. Furthermore, Applicant contends that the Examiner has not provided evidence that other RGD sequence motifs will not work as claimed in view of the knowledge in the art. The Applicants are not claiming "any" sequence having the amino acids RGD. Rather, the Applicants are claiming RGD motifs. To sustain the rejection, the Examiner must provide evidence that the range of RGD motifs described in the Specification and known in the art would not work with the invention as claimed. For example, the Examiner has not provided evidence that a skilled artisan would be unable to select components that will function with the range of RGD motifs described in the Specification and known in the art.

Again, Applicant is relying upon certain biological activities and the disclosure of a single species to support an entire genus. While the Examiner acknowledged that the RGD motifs were well known in the art at the time of the invention, and RGD motifs are bound by surface integrin receptors expressed on endothelial cells. However, the specialized medical literature contains hundreds of reports indicating many RGD-related peptides with different activities and different efficacy. The use of peptides containing the RGD motif has been proposed in several pathologic conditions, with different activities including anti-angiogenesis, anti-thrombotic and anti-metastatic action. The specification fails to provide guidance that the anti-thrombotic/anti-metastatic RGD motifs would be also us to in vivo image tumor that is undergoing neovasculaization. The specification does not provide guidance that an RGD motif with one activity can be use for another activity with the same efficacy. Contrary to Applicant's contentions, the claims as written recite any sequence having RGD sequence. There is insufficient guidance as to which amino acid segments within the polypeptide can be unique and retain a distinct functional capability of "RGD motif-comprising polypeptide". Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495)

7. Claims 87, 92, 96 and 97 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 9/24/03.

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (RGD comprising sequences) to describe the claimed genus, nor does it provide a description of structural features that are common to species (RGD motif). The specification provides no structural description of RGD motifs other than SEQ ID NO: 1; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed RGD comprising sequences looks like. The specification's disclosure is inadequate to describe the claimed genus of polypeptides comprising RGD motif.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 76, 80, 82-84, 87, 91-92 and 96-98 stands rejected under 35 U.S.C. 103(a) as being obvious over U.S Patent No. 5,650,135 (IDS reference AB), in view of U.S Patent No. 6,087,476 (IDS reference AA) and U.S Patent No. 6,180,084 (of record) for the same reasons set forth in the previous Office Action mailed 9/24/03.

Applicant's arguments, filed 4/01/04, have been fully considered, but have not been found convincing.

Applicant argues that there was no reasonable expectation of success that combining the '135 patent with the '476 patent and '084 patent in the manner suggested by the Examiner would result in Claims 76, 80, 82-84, 87, 91, 96-98. The Examiner argues, "From the combined

teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention." Office Action, page 8. However, the Examiner simultaneously emphasizes in the 35 U.S.C. 112 rejections that prior art involving RGD sequences is unpredictable. In particular, the Examiner states, "there is insufficient guidance as to which amino acid segments within the polypeptide can be unique and retain a distinct functional capability of "RGD motif-comprising polypeptide." Ngo et al teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute." Office Action, page 4. Applicant further argues that the Examiners arguments that RGD related art is unpredictable with the statement, "since the amino acid sequence of a polypeptide determined its structural property, predictability of which amino acid fragment can retain the functional capabilities of the R/D motif-comprising polypeptide requires knowledge of, and guidance with regard to, which segments in the polypeptides sequence contribute to its function." Office Action, page 4. Applicant further states that the Examiner purports, "Minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Therefore, structurally unrelated compounds comprising any 'RGD sequence' would be expected to have greater differences in their activities." Office Action, page 4. Combination of the `135 patent with the `084 patent with the technique presented in the `476 patent would require that amino acid sequences be combined with alternate amino acid sequences resulting in the creation of a chimeric molecule. Applicant states that according to the Examiner, this is a highly unpredictable endeavor. Thus, the Examiner's positions in the l 12 and 103 arguments are incompatible. In view of the Examiner's 112 position, the 103 rejection must be withdrawn.

The Examiner recognizes that the dual rejections under the prior art and under enablement may appear to put the applicant in what he may consider to be an untenable position, especially given the fact situation presented here, where the teachings of the specification appear to be commensurate with the teachings of the prior art. It is this type of circumstance, however, that it is especially important for the examiner to make both the enablement rejection and the art rejection of record. Because the teachings of the specification do not appear to add anything further to the teachings of the prior art, if the specification is enabling, the prior art is also enabling, and if the prior art is not enabling, neither is the specification. The burden is thus placed on applicant, and properly so, to point out how the teachings of the specification go beyond those of the prior art. In the instant case, the specification is enabled for the a chimeric polypeptide wherein the chimeric molecule comprises bioluminescent polypeptide RGD motif-comprising polypeptide of SEQ ID NO:1 for the method of in vivo imaging. Therefore, the Examiner does not understand Applicant's arguments.

Applicant argues that claims 76, 80, 82-84, 87, 91-92 and 96-98 are non-obvious. A *prima facie* showing of obviousness requires that an Examiner make a showing of the teaching or motivation

to combine prior art references. In re Dembiczak, 175 F.3d 994, 999 (Fed.Cir. 1999) (emphasis provided). Applicant submits that by making these conclusory statements, the Examiner has not provided any evidence as to why a skilled artisan would make the combination; he has only stated what he believes each reference teaches in isolation from the other references and then stated that it would be obvious to combine the elements. In order to support the combination, the Examiner has merely relied on the level of skill in the art. This is not permissible.

Contrary to Applicant's arguments the examiner relied on evidence to combine the prior art teachings for a *prima facie* of obviousness. In the instant case, while the `135 patent does not expressly teach the specific chimeric molecule comprising a first domain comprising a bioluminescent or luciferase protein and a second domain comprising an RGD motif-comprising polypeptide of SEQ ID NO: 1, but otherwise teaches all of the claimed elements of the claimed a method of in vivo imaging using conjugates contain a biocompatible entity and a light-generating moiety. Light-generating moieties are typically molecules or macromolecules that give off light. They may generate light as a result of radiation absorption (e.g. fluorescent or phosphorescent molecules), or as a result of a chemical reaction (e.g. bioluminescent proteins). Exemplary light-generating moieties are bioluminescent proteins, such as luciferase and aequorin (column 2 lines 63-67 and column 3 lines 1-5 in particular). Luciferases require a substrate, such as luciferin (column 10, lines 33-35 in particular). The `084 patent teaches a tumor homing molecule is linked to a moiety that is detectable external to the subject, thereby providing a composition useful to perform an in vivo diagnostic imaging study. For example, in vivo imaging using a detectable labeled tumor homing peptide can identify the presence of a tumor in a subject (column 37, lines 4-9 in particular). A tumor homing molecule binds specifically to a sample of the tumor obtained from the patient. For example, the RGD-4C (CDCRGDCFC; claimed and reference SEQ ID NO:1) binds to blood vessels in microscopic sections of human tumors, whereas little or no binding occurs in the blood vessels of non-tumor tissues (column 25, lines 46-52 in particular). Furthermore, tumor homing molecules can bind to the endothelial lining of small blood vessels of tumors. The vasculature within tumors is distinct, presumably due to the continual neovascularization, resulting in the formation of new blood vessels required for tumor growth. The distinct properties of the angiogenic neovasculature within tumors are reflected in the presence of specific markers in endothelial cells and pericytes (column 35, lines 44-50 in particular). The `476 patent teaches chimeric proteins obtained by genetic engineering. Such chimeric proteins comprise a continuous polypeptide sequence in which a photoprotein is linked to an antigenically active protein or fraction thereof. The `476 patent further teaches that chimeric proteins which comprise a continuous polypeptide sequence in which a photoprotein is linked to a protein with specific affinities for analytes of interest and methods of using these proteins in immunodiagnostic or imaging processes (column 1, lines 15-28 in particular). The chimeric protein constructed as a continuous polypeptide sequence and comprised of a photoprotein and a second protein. The photoprotein is a protein having luminescent properties and is typically chosen from a class of compounds known as luciferases.

Since claimed SEQ ID NO:1, a tumor homing molecule, binds to blood vessels in microscopic sections of human tumors, whereas little or no binding occurs in the blood vessels of non-tumor tissues (the `084 paten, col. 25, lines 46-52 in particular), And since the `476 patent teaches that

chimeric proteins which comprise a continuous polypeptide sequence in which a luciferase is linked to a protein with specific affinities for analytes of interest and methods of using these proteins in imaging processes (column 1, lines 15-28 in particular). It would have been obvious to one of ordinary skill in this art at the time the invention was made who wants to do non-invasive imaging of a cells comprising tumor cells, wherein said tumor cells are undergoing neovasculaization, to conjugate the tumor homing molecule of SEQ ID NO: 1 taught by `084 patent with the luciferase taught by the `476 patent, which can be use in imaging processes, and use the resultant chimeric molecule in a method of in vivo imaging taught by the `135 patent.

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
July 22, 2004

Christina Chan

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